REMARKS

Consideration of this application in view of the amendments above and the discussion below is respectfully requested.

Claims 49-57 and 59-84 are pending. Claim 58 is canceled. Applicants acknowledge the Examiner's indication that claims 54, 57, 63, 65, 66 and 73 would be allowable if rewritten in independent form including all the limitations of the base claim and any intervening claims. Amendments to claims 54, 55, 63 and 64 have been made to correct improper antecedence and claim dependencies. Amendment to claim 56 is to more particularly define the invention. Appendix I provides the marked-up version of the amended claims. The amendments to the specification are to properly identify government support and the text to the respective figure in Figures 15A through 15D.

Applicants believe that no new matter has been introduced by the amendments made herein.

I. The Amendments

Support for the amendments to the noted claims is found in the properly identified claim. Support for the amendments is found in the reformatted figures originally on two pages 15A and 15D to four pages 15A through 15D.

With regard to the comments, objections and rejections presented in the Action by the Examiner, Applicants' response continues below.

II. Priority and Related Amendment

The Examiner has requested that the specification be amended to recite prior applications and related priority information. Applicants have provided the enclosed Application Data Statement (ADS) in compliance with 37 CFR §1.76. The ADS provides the priority information that need not otherwise be made part of the specification. The present national stage application was filed before November 29, 2000, the effective date of compliance with 37 CFR §1.78(a)(2) in which the claim for

priority must be made within the later of four months from the filing date of the present application or sixteen months from the filing date of the prior application. Therefore, no petition is required to present the claim for priority in the ADS. Applicants request the Examiner evaluate the amended priority claims as recited on page 5 of the ADS. Applicants request that the amended priority claim be entered to include priority to the Non-provisional Application, 08/514,799, filed August 14, 1995, now abandoned, and to the Continuation-in-Part Non-provisional International Application PCT/US96/13194 designating the United States, filed August 13, 1996. This latter application is the parent application to the International Application PCT/US97/09099, from which the present national stage application was designated and filed.

In response to the Examiner's request, Applicants are providing a copy of the Provisional Application No. 60/60/015,869, filed on May 31, 1996. The Examiner stated in paragraph 3 of the Action that the priority date granted to the application is May 30, 1997, the filing date of PCT/US97/09099. The Examiner further states in the same paragraph that sequences disclosed in SEQ ID NOs 7, 9 and 11-22 are not supported in the Provisional Application 60/018,773, filed May 31, 1996. The Examiner did not have a copy of Provisional Application 60/015,869, filed May 31, 1996, to which benefit is claimed, which would allow the Examiner to determine the support to the claimed sequences. Applicants have provided a copy of the latter Provisional Application.

Regarding the specifically disclosed sequences listed above, Applicants direct the Examiner's attention to the following documents and indicated pages in which the sequences were first disclosed: 1) SEQ ID NO 7 - Parent priority patent Non-provisional Application, 08/514,799, filed August 14, 1995, now abandoned, see page 70, line 28; and 2) SEQ ID NO 17 - Provisional Application, 60/015,869, see page 3, line 23. As noted above, Applicants have amended the priority claim to include, with the claims already of record, the added priority claims to the Non-provisional Application, 08/514,799, filed August 14, 1995, now abandoned, and to the Continuation-in-Part Non-provisional International Application PCT/US96/13194 designating the United States, filed August 13, 1996. Applicants contend that the

presently claimed $\alpha_v\beta_5$ antagonist that inhibits angiogenesis is supported in Non-provisional Application, 08/514,799, filed August 14, 1995, beginning at page 34, line 2, continuing to page 35, line 9, page 41, lines 6-23, page 62, lines 6-29, and page 69, beginning at line 4, continuing to page 71, line 3. The specification describes an $\alpha_v\beta_5$ antagonist as compounds that interact with $\alpha_v\beta_5$ receptor in a manner such that functional interactions with the natural $\alpha_v\beta_5$ ligands are interfered. An $\alpha_v\beta_5$ antagonist includes analogs of $\alpha_v\beta_5$ receptor derived from the ligand binding site of the $\alpha_v\beta_5$ receptor, mimetics of either $\alpha_v\beta_5$ or the natural ligand thereof that mimics the structural region involved in the binding interactions, polypeptides that so function including an RGD-containing peptide both in linear and cyclic conformations, polypeptide and organic molecules referred to as an $\alpha_v\beta_5$ mimetic, and an anti-$\alpha_v\beta_5$ monoclonal antibody. The presently claimed methods of using $\alpha_v\beta_5$ antagonist is also supported in Non-provisional Application, 08/514,799, filed August 14, 1995, beginning at page 19, line 26, continuing to page 33, line 3. Applicants further contend that matrix metalloproteinase (MMP-2) derived polypeptides that are broadly recited, including that in SEQ ID NO 17, are supported by the Provisional Application 60/015,869, as disclosed in the specification beginning at page 2, line 34, continuing to page 5, line 10.

In view of the description of $\alpha_v\beta_5$ antagonist and uses thereof supported by the Non-provisional Application, 08/514,799, filed August 14, 1995, Applicants request that the present application and the broadly claimed composition and methods reciting an $\alpha_v\beta_5$ antagonist, including being defined as a MMP-2 polypeptide, a polypeptide, a derivatized polypeptide, a cyclic polypeptide, a monoclonal antibody and an organic mimetic, be granted the priority August 14, 1995 priority date. Applicants further request that the specifically claimed MMP-2 polypeptides be granted, at the least, the priority date of the Provisional Application 60/015,869, filed May 31, 1996.

III. Objections to the Specification

The Examiner requested that the specification be amended to reflect reference to prior applications. The submitted ADS provides the requested reference and the priority claim as discussed above.

The Examiner further objected to the specification in lacking description to support specifically identified figures. The Examiner states that Figures 7A-7E require separate description. Applicants direct the Examiner to page 7, lines 23-28 and specifically to lines 27 and 28, where the specification describes the results of angiogenesis assays with either antibodies or calphostin C on cytokine-induced angiogenesis. As stated on lines 27 and 28, "Figures 7A-7E respectively show angiogenesis induced with bFGF, TNF-α, VEGF, TGF-α, and PMA." Applicants assert that this description is sufficient to support the separate figures.

For Figures 15A and 15B, Applicants have provided the requested amendments as the figures, originally presented on two pages, were reformatted to four pages, Figures 15A through 15D, as discussed above in the Remarks and Amendments sections.

In view of the foregoing, Applicants request that the objections to the specification be withdrawn.

IV. Abstract

Applicants have provided the requested abstract in the present response and on a separate sheet.

V. Rejection under 35 U.S.C. §112, Second Paragraph

Claims 50, 55, 61 and 64 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The Examiner has indicated that the term "organic mimetic compound" is vague and unclear. Applicants direct the Examiner's attention to specification page 19, lines

11 to 14, and page 31, beginning at line 33 continuing to page 32, line 29. The specification describes $\alpha_v\beta_5$ antagonists as including polypeptides, antibodies and other molecules, designated "mimetics" that have the capacity to interfere with $\alpha_v\beta_5$ function. An antagonist is generically referred to as a mimetic because it possesses the ability to "mimic" an $\alpha_v\beta_5$ ligand involved in the functional interaction of the receptor and ligand by blocking the ligand binding domain of the receptor, thereby interfering with the normal function. A mimetic thus is any molecule that exhibits these properties. The specification describes mimetics as including synthetic peptides, analogs or derivatives thereof, or compounds such as organic-based molecules. The latter are thus referred to as organic mimetics that function as $\alpha_v\beta_5$ antagonists by being a mimetic to a ligand of $\alpha_v\beta_5$. Preferred organic compounds are described in the specification. The term "organic mimetic compound" thus is one category of an $\alpha_v\beta_5$ antagonist for use in the present invention. In view of the support in the specification, Applicants assert that the term "organic mimetic compound" is clear.

The Examiner rejected claims 55 and 64 for improper antecedent. Applicant has amended the claim dependency in those claims as well as in claims 54 and 63.

In view of the comments above, Applicants believe that the rejections for indefiniteness have been overcome.

VI. Rejections under 35 U.S.C. §102(b)

1. Claims 56 and 58 - Collier et al.

Claims 56 and 58 are rejected under 35 U.S.C. §102(b) as being clearly anticipated by Collier et al. This rejection is respectfully traversed.

The Examiner has rejected the above claims on the basis that Collier et al. disclose a polypeptide that includes an amino acid residue sequence shown in SEQ ID NOs 11-14 and 16.

The Collier et al. reference, while describing the complete nucleotide and encoded amino acid residue sequence of human type IV procollagenase cDNA, lacks any description of the presently claimed homologous matrix metalloproteinase (MMP-2)

polypeptides having the specified amino acid sequences. Specifically, the Collier et al. reference identifies the complete amino acid residue sequence of the procollagenase enzyme but does not describe or suggest any fragments of the enzyme. In view of the recited structural characteristics of the polypeptides in amended claim 56, Applicants assert that the polypeptides as limited to particular MMP-2 fragments are not anticipated by the Collier et al. reference.

In view of the foregoing, Applicants contend that the rejection for anticipation by Collier et al. has been overcome. Applicants respectfully request that the rejection on this ground for claim 56 be withdrawn and the claim pass on to allowance.

2. Claims 56 and 58 - Chen et al.

Claims 56 and 58 are rejected under 35 U.S.C. §102(b) as being clearly anticipated by Chen et al. This rejection is respectfully traversed.

The Examiner has rejected the above claims on the basis that Chen et al. disclose a polypeptide that includes an amino acid residue sequence shown in SEQ ID NOs 18, 19, 20, 21 and 22.

The Chen et al. reference, while describing the complete cDNA nucleotide and encoded amino acid residue sequence of chicken metalloproteinase, lacks any description of the presently claimed matrix metalloproteinase (MMP-2) polypeptides having the specified amino acid sequences. Specifically, the Chen et al. reference identifies the complete amino acid residue sequence of the MMP-2 gelatinase enzyme but does not describe or suggest any fragments of the enzyme. In view of the recited structural characteristics of the polypeptides in amended claim 56, Applicants assert that the polypeptides as limited to particular MMP-2 fragments are not anticipated by the Chen et al. reference.

In view of the foregoing, Applicants contend that the rejection for anticipation by Chen et al. has been overcome. Applicants respectfully request that the rejection on this ground for claim 56 be withdrawn and the claim pass on to allowance.

3. Claims 60, 62, 71, 72 and 82-84 - Friedlander et al.

Claims 60, 62, 71, 72 and 82-84 are rejected under 35 U.S.C. §102(b) as being clearly anticipated by Friedlander et al. This rejection is respectfully traversed.

The Examiner alleges that Friedlander et al. describe the claimed methods in the rejected claims. The present application is supported by and claims priority to Non-provisional Application, 08/514,799, filed August 14, 1995. The disclosure of an angiogenesis-inhibiting $\alpha_v\beta_5$ antagonist and methods of using thereof is provided in the priority document, the filing date of which precedes the publication date of Friedlander et al. Moreover, the priority document was filed in advance of and is based upon the technology disclosed in Friedlander et al. Therefore, in view of the valid priority to the parent patent application, the present anticipation rejection is not applicable.

In view of the foregoing, Applicants assert that the rejection for anticipation by Friedlander et al. has been negated. Applicants respectfully request that the rejection on this ground for claims 60, 62, 71, 72 and 82-84 be withdrawn and the claims pass on to allowance.

VII. Rejection under 35 U.S.C. §103(a)

1. Claims 49 and 51-53

Claims 49 and 51-53 are rejected under 35 U.S.C. §103 as being unpatentable over Friedlander et al. This rejection is respectfully traversed.

The Examiner contends that the present invention is obvious in view of Friedlander et al. reference for the reasons stated in Section VI above with the exception that the reference does not describe an article of manufacture. Applicants contend that Friedlander et al. disclose the seminal basic research findings of the role of $\alpha_v\beta_5$ receptors in mediating angiogenesis and inhibition thereof with $\alpha_v\beta_5$ antagonists. Friedlander et al. do not disclose the requisite pharmaceutical formulations, do not disclose the dosages related to particular indications that are necessitated in an article of manufacture, and do not suggest an article of manufacture. A *prima facie* obviousness rejection cannot stand if the cited art does not suggest or

motivate one to modify the art to reach the claimed invention. "The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." *In re Gordon*, 733 F.2d 900, 902, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984). The suggestion or motivation must be in the art and not cannot derive from the Applicant's specification in hindsight. Applicant's argue that the cited reference does not provide any basis for arriving at the present invention of an article of manufacture as a whole.

Therefore, in view of the foregoing, Applicants contend that the rejection for obviousness of the rejected claims is negated. Applicants thus respectfully request that the rejection for obviousness be withdrawn and the claims pass on to allowance.

2. Claims 49, 50 and 59

Claims 49, 50 and 59 are rejected under 35 U.S.C. §103 as being unpatentable over Collier et al. and Chen et al. This rejection is respectfully traversed.

The Examiner alleges that the disclosure of the complete nucleotide and encoded amino acid sequences in both Collier et al. and Chen et al. render the present invention *prima facie* obvious regardless of the claimed article of manufacture.

Before the PTO can combine the disclosures of two or more prior art references to render the instant claims obvious, the prior art must contain some suggestion for doing so. *In re Fine*, 837 F.2D 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988). Moreover, the court has recently ruled that the motivating suggestion must be explicit. *Winner International Royalty Corp. v Wang*, No 96-2107, 48 USPQ2d 1139 (D.C.D.C. 1998). In the present rejection, no such explicit motivation can even be manufactured from the teachings of either Collier et al. or Chen et al. that both do not describe any polypeptide fragments of the enzymes useful as $\alpha_v\beta_5$ antagonists in inhibiting angiogenesis. In addition, the cited references do not disclose the requisite pharmaceutical formulations, do not disclose the dosages related to particular indications that are necessitated in an article of manufacture, and do not suggest an article of manufacture. Neither reference provides any teaching, suggestion or

motivation, explicit or vague, of an $\alpha_v\beta_5$ antagonist, moreover an MMP-2 derived polypeptide, as a pharmaceutical and for use in an article of manufacture. One of ordinary skill in the art would not be motivated by the teachings of either Collier et al. or Chen et al. to arrive at the present invention as a whole for the purposes stated by the Examiner.

Therefore, in view of the foregoing, Applicants contend that the rejection for obviousness of the rejected claims is overcome. Applicants thus respectfully request that the rejection for obviousness be withdrawn and the claims pass on to allowance.

3. Claims 67-70, 80 and 81

Claims 67-70, 80 and 81 are rejected under 35 U.S.C. §103 as being unpatentable over Friedlander et al. This rejection is respectfully traversed.

The Examiner contends that the present invention is obvious in view of Friedlander et al. reference for the reasons stated in Section VI above with the exception that the reference does not describe the claimed method where the affected tissue is arthritic or retinal. The present application is supported by and claims priority to Non-provisional Application, 08/514,799, filed August 14, 1995. The disclosure of an angiogenesis-inhibiting $\alpha_v\beta_5$ antagonist and methods of using thereof is provided in the priority document, the filing date of which precedes the publication date of Friedlander et al. Moreover, the priority document was filed in advance of and is based upon the technology disclosed in Friedlander et al. The rejection for *prima facie* obviousness is not applicable in view of the support in the priority document to the claimed methods on which the present rejected claims derive the benefit.

Therefore, in view of the foregoing, Applicants contend that the rejection for obviousness of the rejected claims is negated. Applicants thus respectfully request that the rejection for obviousness be withdrawn and the claims pass on to allowance.

4. Claim 74

Claim 74 is rejected under 35 U.S.C. §103 as being unpatentable over Friedlander et al. in view of U.S. Patent Number 5,567,693. This rejection is respectfully traversed.

The Examiner contends that the present invention is obvious in view of Friedlander et al. reference for disclosing methods of inhibiting angiogenesis and combined with the teachings in the cited patent to administering chemotherapeutic agents. The present application is supported by and claims priority to Non-provisional Application, 08/514,799, filed August 14, 1995. The disclosure of an angiogenesis-inhibiting $\alpha_v\beta_5$ antagonist and methods of using thereof in conjunction with chemotherapy is provided in the priority document, the filing date of which precedes the publication date of Friedlander et al. Moreover, the priority document was filed in advance of and is based upon the technology disclosed in Friedlander et al. The rejection for *prima facie* obviousness is not applicable in view of the support in the priority document to the claimed methods on which the present rejected claims derive the benefit.

Therefore, in view of the foregoing, Applicants contend that the rejection for obviousness of the rejected claims is negated. Applicants thus respectfully request that the rejection for obviousness be withdrawn and the claim pass on to allowance.

5. Claims 75-79

Claims 75-79 are rejected under 35 U.S.C. §103 as being unpatentable over Friedlander et al. This rejection is respectfully traversed.

The Examiner contends that the present invention is obvious in view of Friedlander et al. reference for disclosing methods of inhibiting angiogenesis in particular dosage formulations. The present application is supported by and claims priority to Non-provisional Application, 08/514,799, filed August 14, 1995. The disclosure of an angiogenesis-inhibiting $\alpha_v\beta_5$ antagonist and methods of using thereof in conjunction with dosage formulations and routes of administration is provided in the

priority document, the filing date of which precedes the publication date of Friedlander et al. Moreover, the priority document was filed in advance of and is based upon the technology disclosed in Friedlander et al. The rejection for *prima facie* obviousness is not applicable in view of the support in the priority document to the claimed methods on which the present rejected claims derive the benefit.

Therefore, in view of the foregoing, Applicants contend that the rejection for obviousness of the rejected claims is negated. Applicants thus respectfully request that the rejection for obviousness be withdrawn and the claims pass on to allowance.

VIII. Summary

Applicants believe that a complete response is provided in the foregoing amendments and remarks to each issue and grounds for rejection and objection raised by the Examiner. Applicants submit that patentable subject matter exists with regard to the pending claims and therefore respectfully requests favorable action and entry of the presents Amendments and Response. The application is now believed to be in proper condition for allowance and early notification of allowance is earnestly solicited. The Examiner is invited to telephone the undersigned if it would be deemed helpful to advance the application.

Respectfully submitted,

June 6, 2001
Date

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APPENDIX I

IN THE SPECIFICATION

Please enter the amendments to the specification below.

Please amend the paragraph below filed with the Preliminary Amendment filed on August 27, 1999 as indicated:

At page 1, line 5 of the specification, please insert the amended paragraph:

This invention was made with government support under Contract Nos. [HL54444, CA45726, and CA50826] CA50826, CA45726, HL54444, T32 AI07244-11 and F32 CA72192 by the National Institutes of Health. The government has certain rights in the invention.

At page 8, lines 10-21, please amend the paragraph as indicated:

Figures 15A [and], 15B, 15C and 15D show the consecutive cDNA sequence of chicken MMP-2 along with the deduced amino acid sequence shown on the second line, as shown in Figures 15A, 15B and 15C. The third and fourth lines respectively show the deduced amino acid sequence of human and mouse MMP-2 as described in Example 7. The chicken cDNA sequence is listed in SEQ ID NO 23 along with the encoded amino acid sequence that is also presented separately as SEQ ID NO 24. The numbering of the first nucleotide of the 5' untranslated region and region encoding the proenzyme shown in Figure 15A as a negative number is actually presented as number 1 in Sequence Listing making the latter appear longer than the figure; however, the nucleotide sequence is the figure is identical in length and sequence to that as presented in the listing with the exception of the numbering. Accordingly, references to nucleotide position for chicken or human MMP-2 in the specification, such as in primers for use in amplifying MMP-2 fragments, are based on the nucleotide position as indicated in the figure and not as listed in the Sequence Listing.

At page 42, lines 1-12, please amend the paragraphs as indicated:

** The human MMP-2 amino acid residue sequences for synthetic peptides are indicated by the corresponding residue positions shown in Figures 15A [and 15B]- 15C and also in Figure 16. (MMP-2 refers to a member of the family of matrix metalloproteinase enzymes). The human MMP-2 sequences are listed with the natural cysteine residues but are not listed with engineered cysteine residues as described for the fusion peptides. The non-natural cysteine residues were substituted for the natural amino acid residue at the indicated residue positions in order to facilitate solubility of

the synthetic as well as expressed fusion proteins and to ensure proper folding for presentation of the binding site.
*** The chicken MMP-2 amino acid residue sequences for synthetic peptides are indicated by the corresponding residue positions shown in Figures 15A [and 15B]- 15C. The chicken MMP-2 sequences are listed with the natural cysteine residues but not with the engineered cysteine residues as described for the fusion peptides as described above.

At page 55, lines 12-25, please amend the paragraph as indicated:

The chicken-derived MMP-2 C-terminal domain, also referred to as the hemopexin domain immediately contiguous with the hinge region, comprises the amino acid residues 445-637 of MMP-2. The complete nucleotide and encoded amino acid sequence of chicken MMP-2 is described below and is shown in Figures 15A [and 15B]- 15D, with the nucleotide and amino acid sequences respectively listed as SEQ ID NOs 23 and 24. The human MMP-2 nucleotide and encoded amino acid sequence is also described below, with the latter shown in Figure 16 and SEQ ID NO 25. The C-terminal domain in the human MMP-2 that corresponds to the chicken region of 445-637 begin at amino acid residue 439 and ends with 631 due to six missing residues from the human sequence as shown in Figure[s 15A and 15B]15C. Both human- and chicken-derived C-terminal MMP-2 synthetic peptides for use in practicing the methods of this invention are listed in Table 1. The amino acid residue sequences of the synthetic peptides are the same as those generated by the recombinant fusion protein counterparts but without the GST fusion component. The C-terminal MMP-2 fusion proteins derived from both chicken and human are prepared as described below.

At page 55, beginning at line 29, continuing to page 56, lines 1-12, please amend the paragraph as indicated:

To amplify various regions of chicken and human MMP-2, primer sequences were designed based on the known respective cDNA sequences of chicken and human MMP-2. The complete top strand of the cDNA nucleotide sequence of unprocessed chicken MMP-2, also referred to as progelatinase, is shown in Figures 15A [and 15B]- 15D along with the deduced amino acid sequence shown on the second line (Aimes et al., Biochem. J., 300:729-736, 1994). The third and fourth lines of the figure respectively show the deduced amino acid sequence of human (Collier et al., J. Biol. Chem., 263:6579-6587 (1988)) and mouse MMP-2 (Reponen et al., J. Biol. Chem., 267:7856-7862 (1992)). Identical residues are indicated by dots while the differing residues are given by their one letter IUPAC lettering. Missing residues are indicated by a dash. The numbering of the amino acid residues starts from the first residue of the proenzyme, with the residues of the signal peptide being given negative numbers. The nucleotide sequence is numbered accordingly in the figure although in the Sequence Listing, the first nucleotide is listed as number 1. The putative initation of translation

(ATG) is marked with three forward arrowheads and the translation termination signal (TGA) is indicated by an asterisk. The amino terminal sequences for the chicken proenzyme and active enzyme are contained with diamonds and single arrowheads. As previously stated, the chicken progelatinase nucleotide and amino acid residue sequences are listed together as SEQ ID NO 23 while the encoded amino acid residue sequence is listed separately as SEQ ID NO 24.

At page 56, beginning at line 27, continuing to page 57, lines 1-11, please amend the paragraph as indicated:

From either of the above-described cDNA templates, a number of C-terminal regions of chicken MMP-2, each having the natural cysteine residue at position 637 at the carboxy terminus, were obtained by PCR with the 3' primer listed above (SEQ ID NO 26) paired with one of a number of 5' primers listed below. The amplified regions encoded the following MMP-2 fusion proteins, having sequences corresponding to the amino acid residue positions as shown in Figures [15A and]15B and 15C and also listed in SEQ ID NO 24: 1) 203-637; 2) 274-637; 3) 292-637; 4) 410-637; 5) 445-637. Upstream or 5' primers for amplifying each of the nucleotide regions for encoding the above-listed MMP-2 fusion proteins were designed to encode the polypeptide start sites 3' to an engineered, i.e., PCR-introduced, internal BamHI restriction site to allow for directional ligation into either pGEX-1λT or pGEX-3X expression vectors. The 5' primers included the following sequences, the 5' and 3' ends of which correspond to the indicated 5' and 3' nucleotide positions of the chicken MMP-2 sequence shown in the figure (the amino acid residue position start sites are also indicated for each primer): 1) Nucleotides 599-619, encoding a 203 start site 5'ATGGGATCCACTGCAAATTTC3' (SEQ ID NO 27); 2) Nucleotides 809-830, encoding a 274 start site 5'GCCGGATCCATGACCAGTGTA3' (SEQ ID NO 28); 3) Nucleotides 863-883, encoding a 292 start site 5'GTGGGATCCCTGAAGACTATG3' (SEQ ID NO 29); 4) Nucleotides 1217-1237, encoding a 410 start 5'AGGGGATCCTTAAGGGGATTC3' (SEQ ID NO 30); and 5) Nucleotides 1325-1345, encoding a 445 start site 5'CTCGGATCCTCTGCAAGCACG3' (SEQ ID NO 31).

At page 58, beginning at line 19, continuing to page 59, lines 1-4, please amend the paragraph as indicated:

Briefly, the pGEX-3X plasmid construct encoding the recombinant GST/MMP-2(410-637) fusion protein prepared above was used as a template for amplification according to the manufacturer's protocol for the Expand High Fidelity PCR Kit (Boehringer Mannheim) utilizing a set of oligonucleotide primers whose design was based on the published chicken MMP-2 sequence (also shown in Figures 15A [and 15B]- 15D and in SEQ ID NO 23). One upstream primer, designed to encode a chicken MMP-2 protein start site at position 445 after an engineered internal BamHI

endonuclease restriction site for insertion into the pGEX-3X GST vector, had the nucleotide sequence (5'CTCGGATCCTCTGCAAGCACG3' (SEQ ID NO 32)). The 5' and 3' ends of the primer respectively corresponded to positions 1325-1345 of the chicken MMP-2 sequence in Figure [15A and 15B]15C. Another upstream primer, designed to encode a chicken MMP-2 protein start site at position 516 after an engineered internal BamHI restriction site for insertion into the pGEX-1λT GST vector and to encode a cysteine residue at position 517, had the nucleotide sequence (5'GCAGGATCCGAGTGCTGGGTTTATAC3' (SEQ ID NO 33)). The 5' and 3' ends of the primer respectively corresponded to positions 1537-1562 of the chicken MMP-2 sequence in the figure. A third upstream primer, designed to encode a chicken MMP-2 protein start site at position 549 following an engineered internal EcoRI endonuclease restriction site for insertion into the pGEX-1λT GST vector and to encode a cysteine residue at position 551, had the nucleotide sequence (5'GCAGAATTCAACTGTGGCAGAAACAAG3' (SEQ ID NO 34)). The 5' and 3' ends of the primer respectively corresponded to positions 1639-1665 of the chicken MMP-2 sequence in the figure.

IN THE CLAIMS

54. (Amended) The article of manufacture of claim [49] 50 wherein said cyclic polypeptide comprises the amino acid residue sequence shown in SEQ ID NO 9.

55. (Amended) The article of manufacture of claim [49] 50 wherein said organic mimetic comprises the organic compounds selected from the group consisting of compounds 7, 9, 10, 12, 14, 15, 16, 17 and 18.

56. (Amended) An $\alpha_v\beta_5$ antagonist [comprising] consisting of a matrix metalloproteinase polypeptide [that includes an] with amino acid residue sequence shown in SEQ ID NO 11, 12, 13, 14, 15, 16, 17, 19, 20, 21 or 22.

63. (Amended) The method of claim [60] 61 wherein said cyclic peptide comprises the amino acid residue sequence shown in SEQ ID NO 9.

64. (Amended) The method of claim [60] 61 wherein said organic mimetic comprises the organic compounds selected from the group consisting of compounds 7, 9, 10, 12, 14, 15, 16, 17 and 18.